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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/567,056

06/26/2006

Joachim Schuhmacher

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06/24/2009

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EXAMINER

DO, PENSEE T

ART UNIT

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/567,056	<b>Applicant(s)</b> SCHUHMACHER ET AL.	
	<b>Examiner</b> Pensee T. Do	<b>Art Unit</b> 1641	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 April 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 8-10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☒ Claim(s) 4-6 is/are objected to.
- 8) ☒ Claim(s) 1-10 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/01/06</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Priority***

This application, 10567056, PG Pub. No. 20070111208 filed 06/26/2006 is a national stage entry of PCT/EP04/08708, International Filing Date: 08/04/2004 claims foreign priority to 03018512.8, filed 08/16/2003.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### ***Election/Restrictions***

Applicant's election without traverse of group I, claims 1-7 in the reply filed on April 27, 2009 is acknowledged.

Claims 1-7 are being examined.

Claims 8-10 are withdrawn from further consideration.

### ***Information Disclosure Statement***

The IDS submitted on February 1, 2006 has been acknowledged and entered.

### ***Claimed Invention***

1. Method for the determination of the free fraction of a substance comprising  
(a) incubation of the substance with a suspension of particles, other than erythrocytes, having a lipophilic surface, in a substantially protein-free aqueous medium, for the determination of the distribution of the substance between the particles and said substantially protein free medium;  
b) incubation of the substance with a suspension of particles, other than

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erythrocytes, having a lipophilic surface, in a protein-containing aqueous medium, for the determination of the distribution of the substance between the particles and said protein-containing aqueous medium; and  
(c) determination of the free fraction of the substance from the distributions determined under (a) and b).

### ***Claim Objections***

Claims 4-6 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Claims 4-6 depend from multiple dependent claim 3.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 is indefinite because while reciting in the preamble "a method for the determination of the free fraction..." it fails to recite active method steps.

Claim 1 seems to omit a step of "determining the distribution after each step a) and b).

Claim 2 seems to recite a Markush group. If so, please use appropriate Markush language, i.e. selected from ***a group consisting*** of A, B and C.

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Claims 1 and 4 are indefinite for reciting "substantially protein-free medium" because it is unclear what is meant by "substantially". Is it free of protein or there is still a small non-detectable amount of protein.

Claim 4 is also indefinite because it depends from claim 3 which does not recite protein-free aqueous medium.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Schuhmacher et al. (Journal of Pharmaceutical Sciences, Vol. 89, No. 8, August 2000, pg1008-1121 -- submitted by Applicants).

Schuhmacher teaches a method of determining the free fraction and relative free fraction of Drugs strongly bound to plasma proteins for different species. The Method comprises : a/. determining the membrane affinity in plasma of said substance for a first species; b/. determining the membrane affinity in plasma of said substrate for a second species; c/. determining the relative free fraction from the results determined under steps a and b. (see abstract; pp. 1009, second column, paragraphs 1 & 2).

### ***Claim Rejections - 35 USC § 103***

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veronese et al. (Br. J. Clin. Pharmac (1988), 26, 721-731—submitted by applicants) in view of Loidl-Stahlhofen et al. (Journal of Pharmaceutical Sciences, vol. 90, NO. 5, May 2001, pp. 599-606 – submitted by applicants).

Veronese teaches a method of measuring the unbound or free fraction of a substance/drug. The method comprises incubating the drug with erythrocytes in a buffer (protein-free aqueous medium) and incubating the drug with erythrocytes in plasma; determining the ratio of drug concentrations in erythrocytes and plasma (E/P) and the erythrocytes/buffer concentration ratio are calculated. The unbound/free fraction of drug ( $f_u$ ) in plasma can then be calculated. (see pp. 723- erythrocytes partitioning).

For claim 3, the protein-containing aqueous is plasma.

For claim 4, the protein-free aqueous is buffer. (see pp. 723).

However, Veronese fails to teach incubation of the drug with a suspension of particles in plasma and in buffer. Veronese also fails to teach the particles can be a particle having solid core, silica bead or Transil particles.

Loidl-Stahlhofen teaches that quantification of membrane affinity is an important early screening step in modern drug design. Drugs can be tested for their lipophilicity using lipid membrane models. Loidl-Stahlhofen discovers that Transil particle is a good

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lipid membrane model to test drug or to measure the membrane affinity of drug. (see abstract).

Thus, it would have been obvious to one of ordinary skills in the art to combine the Transil particles taught by Loidl-Stahlhofen with the drug in plasma and in buffer in order to determine the free fraction of the drug as taught by Veronese. When drug is taken into a patient body, it has to adsorb through different membranes, i.e. lipid before binding to its molecular target. Thus, testing for the membrane affinity for drug is also a factor in determining the free fraction of a drug.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Veronese et al. in view of Loidl-Stahlhofen et as applied to claim 1, and further in view of Leung (US 6977305).

Veronese and Loidl-Stahlhofen have been discussed above.

However, they fail to teach the incubations of said substance occur on a plate having multiple cavities or on a 96-well plate or the particle solid core is a ferromagnetic core.

Leung teaches that high-throughput screening such as drug screening is carried out using microwell plate (See col. 23, line 55-col. 24, line 2).

Since Loidl-Stahlhofen teaches that solid supported lipid membranes allow a fast and reliable quantification of membrane affinity, enabling high-throughput screening of this physicochemical parameter. (see abstract), microwell plate is well known (as taught by Leung, as a matrix for high-throughput screening such as drug screening, it

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would have been obvious to one of ordinary skills in the art to carry out incubations on microwell plates.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Veronese et al. in view of Loidl-Stahlhofen as applied to claim 1, and further in view of Kirpotin (US 5,411,730).

Veronese and Loidl-Stahlhofen have been discussed above but fail to teach the particle having a solid core which is ferromagnetic core.

Kirpotin teaches using lipid bilayer ferromagnetic core to study membrane affinity of the drug. (see col. 13, lines 60-col. 14, line 14; col. 20, lines 14-46).

It would have been obvious to one of ordinary skills in the art to use the particle comprising a bilayer lipid coating and a ferromagnetic core as taught by Kirportin in the method of Veronese and Loidl-Stahlhofen so that the ability of the drug to absorb across the lipid bilayer of the particles can be studied.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Pensee T. Do/  
Examiner, Art Unit 1641

/Mark L. Shibuya/  
Supervisory Patent Examiner, Art Unit 1641